JACC: ADVANCES VOL. 3, NO. 11, 2024
© 2024 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ORIGINAL RESEARCH

Characteristics and Outcomes of Patients With Valvular Cardiogenic Shock

Raunak M. Nair, MD,[a] Sanchit Chawla, MD,[b] Feras Alkhalaileh, MD,[c] Bahaa Abdelghaffar, MD,[c] Agam Bansal, MD,[a] Andrew Higgins, MD,[a] Ran Lee, MD,[a] Penelope Rampersad, MD,[a] Umesh.N. Khot, MD,[a] Wael A. Jaber, MD,[a] Grant W. Reed, MD,[a] Paul C. Cremer, MD,[a] Venu Menon, MD[a]

ABSTRACT

BACKGROUND The clinical characteristics and outcomes of patients who develop cardiogenic shock (CS) secondary to primary valvular dysfunction (valvular cardiogenic shock [VCS]) remain unclear.

OBJECTIVES The purpose of this study was to describe the cohort of patients with VCS and understand their outcomes compared to other forms of CS.

METHODS All patients admitted to Cleveland Clinic cardiac intensive care unit between January 1, 2010, and December 31, 2021, with a diagnosis of CS were retrospectively identified. Characteristics and outcomes for shock patients with VCS were compared to those without VCS.

RESULTS A total of 2,754 patients were admitted to our cardiac intensive care unit with CS, of which 442 (16%) had VCS. The median age of patients with VCS was higher than those with non-VCS (70 years vs 64 years, $P < 0.001$) and were more likely females (40.3% vs 32.1%, $P = 0.001$). VCS was predominantly due to native valve dysfunction as compared to prosthetic valve dysfunction (71% vs 29%, $P < 0.001$), with the aortic valve noted to be the most common valve affected. Patients with VCS had higher 1-year (44% vs 37%, $P < 0.001$) and 30-day all-cause mortality (28% vs 20%, $P < 0.001$) compared to those without VCS. When compared to percutaneous intervention and medical therapy alone, surgical intervention in VCS was associated with the best short- and long-term outcomes ($P < 0.001$).

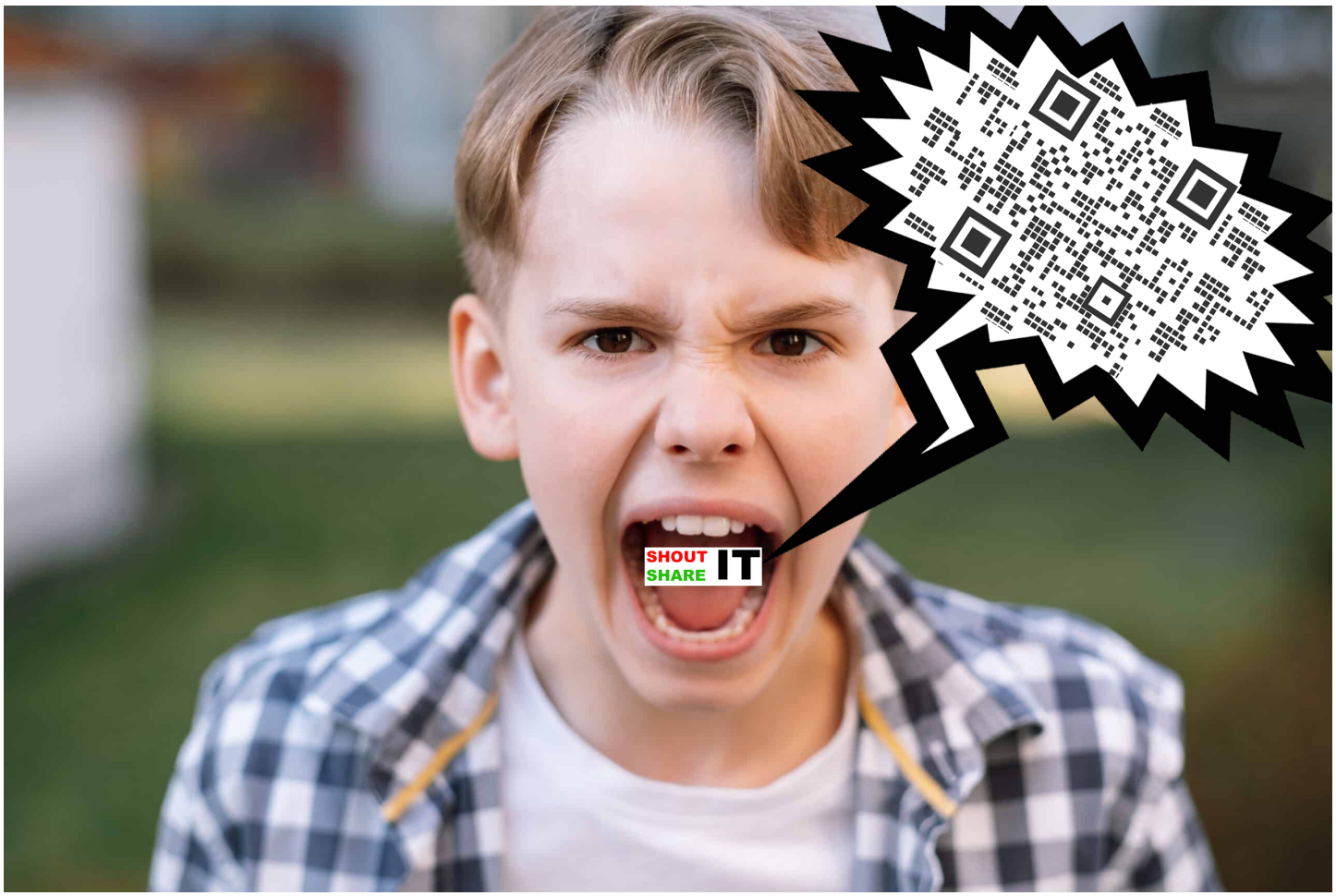
CONCLUSIONS VCS is associated with poor short and long outcomes. Native valvular dysfunction and aortic valve involvement account for the majority of patients with VCS. Definitive surgical therapy and expanding the role of percutaneous therapies may be pivotal in improving clinical outcomes in this high-risk cohort.
(JACC Adv. 2024;3:101303) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiogenic shock (CS) is a heterogeneous clinical entity that remains associated with high in-hospital mortality.[1-3] Few randomized clinical trials have been performed in the area of CS and have predominantly been limited to a post-infarction setting.[4-6] Although CS in the setting of an acute myocardial infarction remains the most common etiology, the incidence of CS due to a primary

From the [a]Cleveland Clinic Heart, Vascular and Thoracic Institute, Cleveland, OH, USA; [b]Cleveland Clinic Critical Care Department, Cleveland, OH, USA; and the [c]Cleveland Clinic Foundation Internal Medicine Department, Cleveland, OH, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 29, 2024; revised manuscript received August 4, 2024, accepted August 13, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101303


SHOUT
SHARE IT

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

CICU = cardiac intensive care unit

CS = cardiogenic shock

EMR = electronic medical record

MR = mitral regurgitation

MS = mitral stenosis

NVD = native valvular dysfunction

VCS = valvular cardiogenic shock

valve dysfunction is rising.[7] Patients with valvular CS (VCS) are a unique, inadequately characterized subset and the real-world outcomes of this cohort have not been previously reported.

The pathogenesis of hemodynamic instability attributable to primary valve dysfunction is heterogeneous. The progression of primary native valve dysfunction is usually an indolent process, with clinical symptoms and ventricular dysfunction developing over several years, or even decades.[8,9] A clinical presentation with hemodynamic instability warranting cardiac intensive care unit (CICU) admission is unexpected in this population, but a lack of a primary diagnosis or inadequate clinical and imaging surveillance, may both result in hospitalization with manifest hemodynamic instability. Acute valvular dysfunction in an unprepared ventricle may often present as CS and is commonly seen with chordal rupture in the background of myxomatous mitral valve disease or due to acute valvular incompetence complicating infective endocarditis.[10,11] Similarly, structural deterioration of bioprosthetic valves is usually an indolent process but can go unappreciated till sudden hemodynamic instability manifests. Rapid degeneration of bioprosthetic valves in vulnerable populations is well described and sudden catastrophic valve failure has been noted in both bioprosthetic and homograft valves.[12-14] While structural failure in mechanical valves is a relative nonentity in the post-Starr Edwards era, the hazard from acute valve thrombosis persists.[15-17] Consequently, with the aging of the population, the fragmented nature of the health care system, the ever-expanding number of patients living with prosthetic heart valves, and the ongoing intravenous drug epidemic, the number of patients presenting with VCS is expected to increase. Recent advancements in percutaneous therapies have also brought forth new definitive treatment options for patients with VCS who are otherwise considered to be at prohibitive surgical risk. In this background, our study aimed to evaluate the incidence, characteristics, and outcomes of consecutive patients with VCS admitted to a quaternary care CICU.

METHODS

STUDY POPULATION. All adults above the age of 18 who were admitted to the Cleveland Clinic CICU with a diagnosis of CS, between January 1, 2010, and December 31, 2021, were retrospectively identified from electronic medical records (EMRs). The CICU at the Cleveland Clinic is a 24-bed closed unit. Patient care in this unit is under the direct supervision of 10 faculty, all of whom have greater than 5 years of experience as ICU staff or are dual board certified in Cardiology and Critical Care. Diagnosis of CS was documented concurrent with patient care in the progress note of the staff physician and made using standard guidelines incorporating either systolic blood pressure <90 mm HG; need for vasopressors/mechanical support to maintain hemodynamic stability or a right heart catheterization with a pulmonary capillary wedge pressure ≥ 15 mm Hg and cardiac index ≤2.2 L/min/m^2 accompanied by signs of impaired end-organ perfusion. Patients with CS were retrospectively stratified into those with VCS or non-VCS depending on the predominant etiology responsible for CS. VCS was defined as the presence of any acute severe primary valvular dysfunction or acute on chronic worsening of primary valvular dysfunction that was implicated as the dominant etiology resulting in CICU admission with CS. Subjects with severe functional mitral regurgitation (MR) attributed to underlying left ventricular dysfunction were not considered to have VCS. Patients with a diagnosis of "mixed shock" as suggested by systemic vascular resistance <800 dyn/s/cm^5 were also excluded. The first comprehensive transthoracic echocardiogram after admission to the CICU was utilized to identify the valve involved (tricuspid, pulmonary, mitral, or aortic), type of valve (native versus prosthetic), and nature of the primary valvular lesion (regurgitation, stenotic, or mixed). The definition of mixed valvular disease is presented in Supplemental Table 1. Baseline characteristics, comorbidities, lab results, in-hospital treatment characteristics, and treatment strategies were collected for all patients from EMRs. The study protocol was approved by our Institutional Review Board, with a waiver of informed consent.

STUDY OUTCOMES. The primary outcome of interest was 1-year all-cause mortality. This outcome was compared between patients with VCS and non-VCS. Patients with VCS were also stratified according to the type of valve involved (into native vs prosthetic), location of the valve involved (into aortic, mitral, tricuspid, or pulmonary), nature of the lesion (regurgitation, stenotic, or mixed), and as per treatment strategy (into medical management, percutaneous therapies or surgery) and outcomes were assessed between the respective cohorts. We also evaluated outcomes between VCS due to the four most prominent valvular conditions: aortic stenosis

(AS), aortic regurgitation (AR), MR, and mitral stenosis (MS). The secondary outcome of interest was 30-day all-cause mortality.

STATISTICAL ANALYSIS. Descriptive statistics were utilized to summarize the data obtained. Continuous variables are presented as median (quartile 1, quartile 3) and were compared using the Wilcoxon rank-sum test or analysis of variance (for >2 groups). Non-normal continuous variables were compared using Kruskal-Wallis test. Categorical data are described using frequencies and percentages and were compared using the chi-squared test. Survival analysis was performed using Kaplan-Meier nonparametric method and comparisons were made using the log-rank test. The date of death was ascertained by a manual search in the EMR. The hazard rates for patients with VCS on survival (30 days and 1 year) were calculated using unadjusted and adjusted Cox regression models. For the Kaplan-Meier time to event analysis and Cox regression models, treatment strategies were stratified into medical therapy, percutaneous therapy, and surgical management. We also created a parsimonious multivariable Cox regression model containing variables relevant to outcomes of patients with CS as evidenced through prior literature and clinical experience, and also included covariates which were found to be associated with the outcome on univariate analysis with $P < 0.20$ in order to assess the adjusted effect of treatment strategies on 1-year all-cause mortality in patients with VCS. In this model, treatment strategies were stratified into medical management or any intervention (which included both percutaneous and surgical therapy) in order to compare the effect between no procedural intervention to any intervention in this cohort. The proportional hazards assumption for the Cox models was verified by generating a plot for each individual predictor in the model and confirming that the slope of each plot was close to zero.

To accommodate for selection bias, we performed 1:1 "greedy" propensity matching without replacement to match all the patients with VCS who received any form of intervention to those who did not. All variables in **Table 1** and the location of the valve involved (tricuspid, pulmonary, mitral, or aortic) were included in the propensity model. Rubin's rules 1 and 2 were checked for passing assumptions and the degree of covariate imbalance was assessed using a "Love plot" in the matched sample (Supplemental Figure 1). A standardized mean difference of <10% was considered acceptable. Conditional logistic regression was performed on this matched sample to assess the difference in probability of primary outcome (1-year mortality), between patients in the two treatment groups (medical management vs any intervention). Since our analysis revealed significant results, a sensitivity analysis for matched binary outcome was performed using Rosenbaum bonds to calculate the sensitivity parameter or "Gamma" to explain the effect of an unmeasured confounder that would bias this effect.[18] All analyses were performed using Rstudio (version 4.1.2, "Prairie Trillium").

RESULTS

INCIDENCE AND BASELINE CHARACTERISTICS OF PATIENTS WITH VCS. During the study period, we identified 2,820 patients with a confirmed diagnosis of CS. We excluded 44 patients who had an initial component of suspected dominant septic shock and 22 patients with incomplete variables from our analysis. The final cohort consisted of 2,754 patients with CS; of which, 442 patients (16%) were found to have VCS and 2,312 (84%) patients had CS due to other causes (non-VCS) (**Figure 1**). **Table 1** reveals comparison of baseline characteristics between CS patients with and without VCS. The group with VCS was noted to be significantly older (70 years vs 64 years, $P < 0.001$) and have a higher prevalence of atrial fibrillation (57.7% vs 48.6%, $P = 0.001$), underlying chronic obstructive pulmonary disease (25.8% vs 20.3%, $P = 0.012$), and history of valve replacement or repair (32.6% vs 8%, $P < 0.001$). Patients with VCS had significantly lower median peak troponin T (0.11 vs 0.41 ng/mL, $P < 0.001$) but higher median peak lactate (4.6 vs 4.2 mmol/L, $P = 0.029$). Subjects admitted with VCS were critically ill with 39.4% requiring mechanical ventilation, 37.6% needing temporary mechanical circulatory support, and 47.3% requiring treatment with a vasopressor or inotropic agent (similar to non-VCS patients).

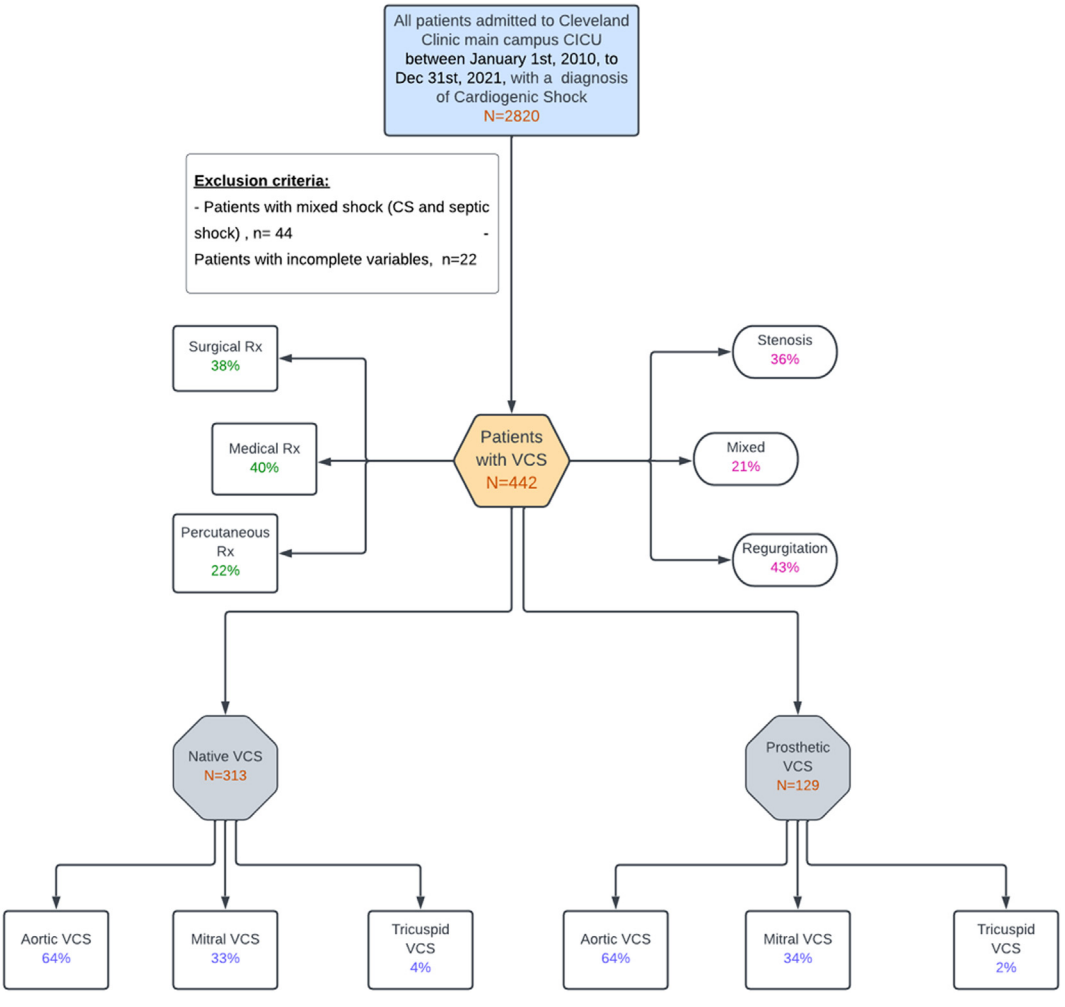
NATURE AND TYPE OF VALVE INVOLVED. Of the 442 patients with VCS, 313 patients (71%) had native valvular dysfunction (NVD) whereas 129 patients (29%) had prosthetic valvular dysfunction (**Figure 1**). The valve in the aortic position (native/prosthetic) was most commonly implicated (64%), compared to the mitral (33%) or tricuspid (3%) position. When compared to subjects with VCS due to prosthetic valve dysfunction, those with NVD were significantly older (median age 72 years vs 66 years, $P = 0.001$), more likely to have underlying chronic kidney disease (45.7% vs 35%, $P = 0.047$), and less likely to have a prior pacemaker or defibrillator implanted (15.7% vs 27.1%, $P = 0.008$). There were no significant

TABLE 1 Baseline Characteristics of Patients Who Had VCS Compared to Those Who Had Non-VCS

	Patients with VCS (n = 442)	Patients with Non-VCS (n = 2312)	*P* Value
Age, y	70.00 (61.00, 80.00)	64.00 (56.00, 73.00)	<0.001
BMI, kg/m^2	27.02 (23.61, 31.94)	28.36 (24.45, 32.97)	0.003
Male	264 (59.7)	1,571 (67.9)	0.001
Race			<0.001
Caucasian	366 (82.8)	1,730 (74.8)	
African American	57 (12.9)	488 (21.1)	
Other	19 (4.3)	94 (4.1)	
Diabetes mellitus	176 (39.8)	977 (42.3)	0.368
Dyslipidemia	213 (48.2)	1,120 (48.4)	0.964
Hypertension	260 (58.8)	1,435 (62.1)	0.218
Atrial fibrillation	255 (57.7)	1,124 (48.6)	0.001
Chronic obstructive pulmonary disease	114 (25.8)	470 (20.3)	0.012
Chronic kidney disease	188 (42.5)	900 (38.9)	0.171
Peripheral arterial disease	155 (35.1)	1,017 (44.0)	0.001
History of myocardial infarction	86 (19.5)	1,059 (45.8)	<0.001
History of coronary artery bypass grafting	77 (17.4)	352 (15.2)	0.274
History of coronary artery disease	250 (56.6)	1,448 (62.6)	0.019
History of stroke/TIA	121 (27.4)	475 (20.5)	0.002
History of pacemaker or defibrillator	84 (19.0)	576 (24.9)	0.009
History of valve replacement or repair	144 (32.6)	184 (8.0)	<0.001
Ejection fraction in CICU	45.00 (27.00, 60.00)	26.00 (18.00, 41.00)	<0.001
Lab values on presentation			
Hemoglobin, g/dl	10.80 (9.40, 12.40)	12.00 (10.30, 13.70)	<0.001
WBC count, k/uL	9.95 (7.35, 14.03)	10.20 (7.43, 14.02)	0.848
Sodium, mmol/L	128.00 (122.00, 132.00)	129.00 (123.00, 132.00)	0.058
Creatinine, mg/dL	2.24 (1.59, 3.60)	2.05 (1.40, 3.42)	0.010
Troponin T, ng/mL	0.11 (0.04, 0.43)	0.41 (0.07, 2.14)	<0.001
NT-proBNP, pg/mL	12,193.00 (5,790.00, 22,171.00)	6,820.00 (3,007.00, 16,257.00)	<0.001
Lactate, mmol/L	4.60 (2.70, 8.40)	4.20 (2.40, 7.60)	0.029
Bilirubin, mg/dL	1.80 (1.10, 3.27)	1.50 (0.90, 2.60)	<0.001
Peak AST, CICU in U/L	85.50 (31.25, 384.50)	90.00 (39.00, 379.50)	0.334
Peak ALT, CICU U/L	132.50 (57.00, 493.25)	145.00 (55.00, 527.00)	0.788
CICU characteristics			
Days in the CICU	16.00 (9.00, 28.00)	16.00 (9.00, 30.00)	0.928
Vasopressors or inotropes[a]	209 (47.3)	1,070 (46.3)	0.737
Right heart catheterization	360 (81.4)	1746 (75.5)	0.009
Mechanical circulatory support	166 (37.6)	843 (36.5)	0.701
Mechanical ventilation	174 (39.4)	812 (35.1)	0.099
Primary valvular dysfunction among patients with VCS (N = 442)			
Mitral regurgitation			114 (26%)
Mitral stenosis			18 (4%)
Mixed mitral valve disease			15 (3%)
Aortic regurgitation			65 (15%)
Aortic stenosis			142 (32%)
Mixed aortic valve disease			75 (17%)
Tricuspid regurgitation			12 (3%)
Tricuspid stenosis			0
Mixed tricuspid valve disease			1 (<1%)

Values are median (Q1, Q3) or n (%). [a]Includes norepinephrine, epinephrine, vasopressin, phenylephrine, dopamine, dobutamine, or milrinone.
BMI = body mass index; CICU = cardiac intensive care unit; TIA = transient ischemic attack; VCS = valvular cardiogenic shock.

FIGURE 1 Study Flowsheet


All patients admitted to Cleveland Clinic main campus CICU between January 1st, 2010, to Dec 31st, 2021, with a diagnosis of Cardiogenic Shock
N=2820
Exclusion criteria:
- Patients with mixed shock (CS and septic shock) , n= 44
- Patients with incomplete variables, n=22
Surgical Rx 38%
Medical Rx 40%
Percutaneous Rx 22%
Patients with VCS N=442
Stenosis 36%
Mixed 21%
Regurgitation 43%
Native VCS N=313
Prosthetic VCS N=129
Aortic VCS 64%
Mitral VCS 33%
Tricuspid VCS 4%
Aortic VCS 64%
Mitral VCS 34%
Tricuspid VCS 2%

CICU = cardiac intensive care unit; CS = cardiogenic shock; VCS = valvular cardiogenic shock.

differences in the utilization of right heart catheterization, mechanical circulatory support, or mechanical ventilation between the two groups.

VALVE LESION AND TREATMENT STRATEGY. A comparison of the type of valvular lesion that was responsible for VCS revealed that regurgitant lesions contributed to the bulk of cases (43%), followed by stenotic lesions (36%), and then mixed lesions (21%). Among subjects with VCS, surgical intervention was performed in 38% of patients, percutaneous intervention in 22%, whereas 40% were managed medically (Figure 1). Of the patients who had a percutaneous intervention (n = 97), 47% had balloon aortic valvuloplasty, 27% had transcatheter aortic valve replacement, 12% patients had a mitral valve intervention, and 11% had multiple valve interventions. The median length of time between CICU admission and a percutaneous intervention was 7 days (IQR: 4-14 days). Comparison of characteristics between patients depending on treatment strategies revealed that patients who received surgical treatment were younger and had significantly fewer comorbidities (Table 2).

ALL-CAUSE MORTALITY. The median survival time for the entire cohort with CS was 1,539 days (Q1, Q3: 1,343, 1,717 days).

The median survival time for VCS patients was 999 days (Q1, Q3: 429, 1,836 days). Overall, the 1-year all-cause mortality was higher for patients with VCS compared to patients with non-VCS (44% vs 37%,

TABLE 2 Baseline Characteristics of Patients With VCS Depending on Treatment Strategy

	Medical Management (n = 168)	Percutaneous Therapy (n = 97)	Surgery (n = 177)	*P* Value
Age, y	72.00 (62.00, 81.00)	77.00 (69.00, 84.00)	64.00 (55.00, 72.00)	<0.001
BMI, kg/m^2	27.09 (23.20, 32.80)	26.60 (23.89, 31.43)	27.37 (23.79, 31.73)	0.932
Male	89 (53.0)	63 (64.9)	112 (63.3)	0.074
Race				0.51
Caucasian	131 (78.0)	89 (91.8)	146 (82.5)	
African American	28 (16.7)	5 (5.2)	24 (13.6)	
Other	9 (5.4)	3 (3.1)	7 (4.0)	
Diabetes mellitus	69 (41.1)	47 (48.5)	60 (33.9)	0.057
Dyslipidemia	76 (45.2)	61 (62.9)	76 (42.9)	0.004
Hypertension	97 (57.7)	67 (69.1)	96 (54.2)	0.054
Atrial fibrillation	93 (55.4)	60 (61.9)	102 (57.6)	0.587
Chronic obstructive pulmonary disease	51 (30.4)	34 (35.1)	29 (16.4)	0.001
Chronic kidney disease	87 (51.8)	48 (49.5)	53 (29.9)	<0.001
History of coronary artery disease	91 (54.2)	71 (73.2)	88 (49.7)	0.001
History of coronary artery bypass grafting	34 (20.2)	24 (24.7)	19 (10.7)	0.007
History of stroke/TIA	41 (24.4)	28 (28.9)	52 (29.4)	0.546
History of pacemaker or defibrillator	33 (19.6)	27 (27.8)	24 (13.6)	0.015
History of valve replacement or repair	41 (24.4)	36 (37.1)	67 (37.9)	0.016
Ejection fraction in CICU	37.00 (24.75, 58.25)	39.00 (24.50, 54.50)	53.50 (35.00, 60.25)	<0.001
CICU characteristics				
Days in the CICU	12.00 (7.00-18.00)	15.00 (9.00-26.00)	22.00 (14.00-43.00)	<0.001
Vasopressors or inotropes	77 (45.8)	38 (39.2)	94 (53.1)	0.078
Right heart catheterization	141 (83.9)	81 (83.5)	138 (78.0)	0.305
Mechanical circulatory support	54 (32.1)	34 (35.1)	78 (44.1)	0.062
Mechanical ventilation	60 (35.7)	31 (32.0)	83 (46.9)	0.025

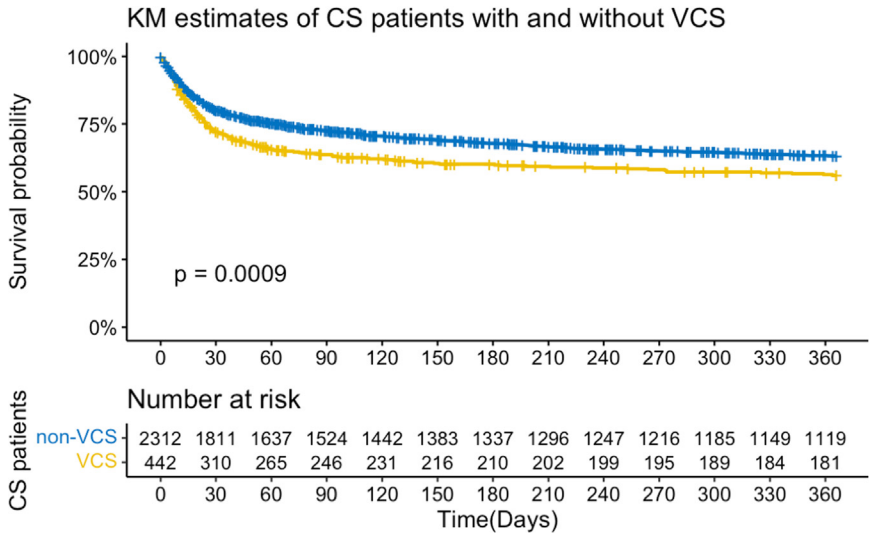
Values are median (Q1, Q3), n (%), or median (IQR).
Abbreviations as in Table 1.

P = <0.001) (Figure 2). Patients with VCS also had higher 30-day mortality compared to those with non-VCS (28% vs 20%, P = <0.001) (Supplemental Figure 2). However, upon adjusting for other covariates, the presence of VCS was not independently associated with higher hazard of 1-year all-cause mortality (adjusted HR: 1.13; 95% CI: 0.96-1.33; P = 0.15). The outcomes for patients with VCS stratified by location, type, and nature of valve lesion are illustrated in Figure 3 and the Central Illustration. Patients with primary aortic valve dysfunction as their etiology had worse outcomes than patients with primary mitral valve disease (Figure 3). Upon comparing the outcomes depending on lesion type, we noted that patients with VCS secondary to a stenotic valvular lesion had the worst outcomes compared to a mixed or regurgitant lesion (Central Illustration). Finally, a comparison of outcomes by treatment strategy revealed that patients with VCS who underwent surgery were less likely to die at 1 year compared to those who underwent medical management or percutaneous therapies (Central Illustration). Multivariable Cox regression revealed that even after adjusting for pertinent variables, patients who were medically managed had a higher hazard of death at 1 year compared to any form of intervention (percutaneous or surgical), with an HR of 3.78 (95% CI: 2.72, 5.27; P < 0.001) (Table 3). This association between medical management and 1-year mortality was similar in the propensity matched cohort (HR: 3.44; 95% CI: 2.16-5.47; P < 0.001). Sensitivity analysis revealed that to explain away the observed association between medical management and the primary outcome (death at 1 year), a hidden bias or unobserved covariate would need to increase the odds of medical management by more than a factor of Γ(Gamma) = 2. Regardless of the type of valve (native/prosthetic), the 1-year all-cause mortality rates for AS, AR, MR, and MS were 55%, 32%, 35%, and 56%. Similarly, the 30-day all-cause mortality rates for AS, AR, MR, and MS were 31%, 21%, 23%, and 50%, respectively (Supplemental Figure 3A and 3B).

DISCUSSION

This analysis represents the largest evaluation of the characteristics and outcomes of patients presenting

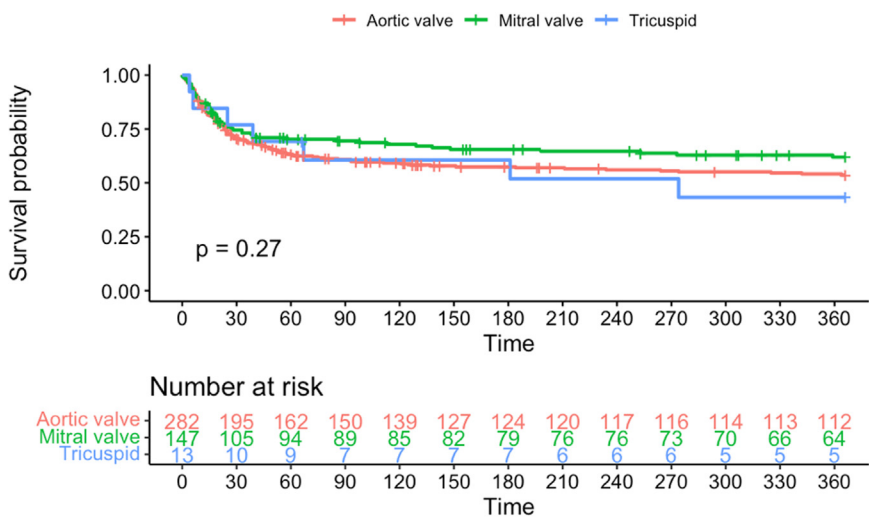
FIGURE 2 1-Year All-Cause Mortality of Patients With and Without VCS Among Patients With CS



Abbreviations as in Figure 1.

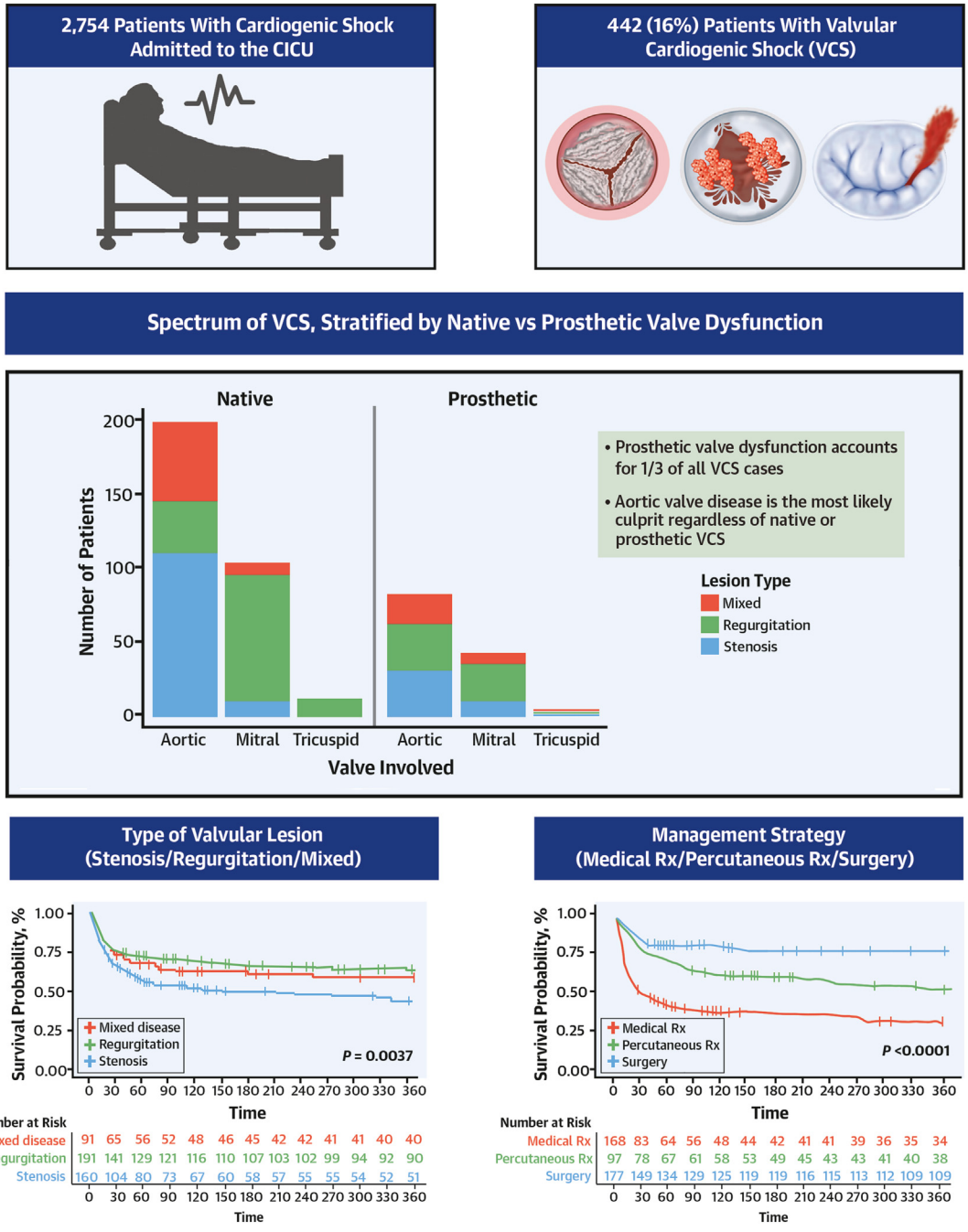
with VCS. Our study reveals several salient findings in this previously poorly defined clinical subset of patients. We observed that a significant proportion of patients with CS (16%) admitted to our CICU had a primary valvular etiology implicated. These subjects were critically ill with high rates of mechanical ventilation, prolonged CICU length of stay, and an observed 1-year mortality rate of 44% that exceeded the mortality rates observed in non-VCS subjects. Secondly, while NVD accounted for the majority of VCS cases, a quarter could be attributed to primary prosthetic valve dysfunction. Pathology in the aortic position was implicated most commonly and regurgitant lesions were the predominant valvular lesion

FIGURE 3 One-Year All-Cause Mortality of Patients With VCS Stratified by the Valve Involved



Abbreviation as in Figure 1.

CENTRAL ILLUSTRATION **Characteristics and Outcomes of Patients With Valvular Cardiogenic Shock**


2,754 Patients With Cardiogenic Shock Admitted to the CICU
442 (16%) Patients With Valvular Cardiogenic Shock (VCS)
Spectrum of VCS, Stratified by Native vs Prosthetic Valve Dysfunction
Native
Prosthetic
Number of Patients
200
150
100
50
0
Aortic
Mitral
Tricuspid
Aortic
Mitral
Tricuspid
Valve Involved
• Prosthetic valve dysfunction accounts for 1/3 of all VCS cases
• Aortic valve disease is the most likely culprit regardless of native or prosthetic VCS
Lesion Type
Mixed
Regurgitation
Stenosis
Type of Valvular Lesion (Stenosis/Regurgitation/Mixed)
Survival Probability, %
1.00
0.75
0.50
0.25
0.00
Mixed disease
Regurgitation
Stenosis
P = 0.0037
0 30 60 90 120 150 180 210 240 270 300 330 360
Time
Number at Risk
Mixed disease 91 65 56 52 48 46 45 42 42 41 41 40 40
Regurgitation 191 141 129 121 116 110 107 103 102 99 94 92 90
Stenosis 160 104 80 73 67 60 58 57 55 55 54 52 51
0 30 60 90 120 150 180 210 240 270 300 330 360
Time
Management Strategy (Medical Rx/Percutaneous Rx/Surgery)
Survival Probability, %
1.00
0.75
0.50
0.25
0.00
Medical Rx
Percutaneous Rx
Surgery
P <0.0001
0 30 60 90 120 150 180 210 240 270 300 330 360
Time
Number at Risk
Medical Rx 168 83 64 56 48 44 42 41 41 39 36 35 34
Percutaneous Rx 97 78 67 61 58 53 49 45 43 43 41 40 38
Surgery 177 149 134 129 125 119 119 116 115 113 112 109 109
0 30 60 90 120 150 180 210 240 270 300 330 360
Time

Nair RM, et al. JACC Adv. 2024;3(11):101303.

Abbreviation as in Figure 1.

observed. Although the majority of subjects presenting with VCS received some form of targeted valve intervention (either surgery or percutaneous therapy), a significant proportion was treated just medically. Furthermore, subjects who received surgical intervention had the best long-term survival when compared to percutaneous intervention and medical management. Finally, the lack of a valve-targeted intervention noted in medically managed patients was associated with the worst observed short- and long-term survival.

Definitive surgical intervention has been the mainstay of treatment for patients with symptomatic valvular dysfunction.[8,19] There is however a paucity of literature reporting on the clinical outcomes of emergent and urgent surgical intervention in critically ill subjects due to valvular heart disease. Despite the acuity of presentation, our data suggest that patients selected to receive surgical intervention have acceptable clinical outcomes. An initial procedural hazard is noted with little additional attrition observed over the period of follow-up. Our data also reveal that despite admission to a high-volume institution, a significant proportion of VCS patients are currently not considered candidates for surgical intervention. The high rates of mechanical ventilation and mechanical circulatory support utilized in these medically treated subjects suggest that the lack of surgical candidacy in this population was not driven by therapeutic inertia but by the inability to deliver successful surgical outcomes in this setting. Although speculative, a missed opportunity for improving surgical candidacy and outcomes with early recognition, referral, and transfer from the community appears to exist.

Over the past decade, advances in transcatheter valve interventions have greatly advanced our ability to deliver definitive valve therapy.[20-23] While evaluation and approval of these devices and procedures have occurred in an elective environment, the utility of these devices in an urgent or emergent setting to improve individual patient outcomes appears obvious, albeit with higher procedural risk.[24-28] Expanding the role and utilization of transcatheter therapies in an emergent setting will undoubtedly serve to expand the population offered definitive valve interventions in this setting and favorable impact on the mortality outcomes currently observed in this group. Prior studies have also shown significantly better outcomes for transcatheter interventions when performed in centers with high procedural volume. Early transfer of these critically ill patients to an experienced valve center could favorably contribute to the prognosis of patients with VCS.[29,30] Outcomes for patients selected to receive a percutaneous valve intervention in our study were intermediate between the rates observed with surgical and medical intervention. The fact that percutaneous treatment strategy in our data set also included temporary salvage interventions such as balloon aortic valvuloplasty in patients who are not good candidates for definitive treatment may have contributed to this finding.

TABLE 3 Association Between Treatment Strategy and 1-Year All-Cause Mortality in Patients With VCS

	Unadjusted		Multivariable-Adjusted Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.04)	<0.001
Male	0.74 (0.55-0.99)	0.040	0.90 (0.67-1.22)	0.501
Body mass index	1.01 (0.99-1.03)	0.171	1.02 (1.00-1.04)	0.103
Diabetes	1.20 (0.90-1.61)	0.215	1.08 (0.79-1.48)	0.612
COPD	1.48 (1.09-2.02)	0.012	1.32 (0.96-1.82)	0.089
CKD	1.58 (1.18-2.10)	0.002	1.15 (0.84 1.56)	0.390
CAD	1.15 (0.86-1.55)	0.347	1.04 (0.75-1.44)	0.808
Medical management[a]	3.64 (2.71-4.89)	<0.001	3.78 (2.72-5.27)	<0.001
Prior valve replacement or repair	0.81 (0.59-1.11)	0.190	1.10 (0.78-1.56)	0.569
CICU days	0.99 (0.98-1.00)	0.056	1.00 (0.99-1.01)	0.626
Pressor or inotrope use	1.35 (1.01-1.80)	0.044	1.48 (1.02-2.16)	0.039
CRRT	1.37 (0.99-1.90)	0.056	1.22 (0.83-1.78)	0.312
Mechanical Ventilation	1.12 (0.84-1.51)	0.437	1.10 (0.75-1.62)	0.612

[a]Treatment strategy here categorized as any intervention (percutaneous/surgical) vs medical management.
CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRRT = continuous renal replacement therapy; other abbreviation as in Table 1.

A quarter of the patients in our study were noted to have VCS secondary to prosthetic valve dysfunction. With the rising prevalence of prosthetic valve use, as evidenced by over 130,00 valve replacements performed in the United States in the aortic position alone in 2019,[31] the incidence of prosthetic valve dysfunction presenting as CS should be expected to rise in the future. Patients with VCS due to prosthetic valve dysfunction are older and have comorbid organ dysfunction which translates to a high risk of perioperative surgical mortality. The evolution of transcatheter valves and the promising results with "valve in valve" procedure represents a definitive and preferable therapeutic option in many of these patients.[32-34]

STUDY LIMITATIONS. Although our study represents the largest analysis of patients with VCS, the results of our study should be interpreted in the context of the following limitations. Firstly, our findings are obtained from observations at a single quaternary care CICU and thus require further validation at other

health care institutions. Secondly, due to the observational nature of our study, the effect of unmeasured covariates cannot be excluded. However, propensity scores were used to match and weight the analysis in an effort to balance the covariates. Sensitivity analysis was also performed to calculate a Gamma value. Thirdly, the diagnosis of VCS was identified retrospectively with the help of EMRs. However, the diagnosis of CS was made in real-time by CICU providers experienced in the management of patients with CS utilizing standardized criteria. In addition, conclusions involving specific subcohorts (such as those with tricuspid-VCS) are limited due to the low number of patients and by excluding patients with systemic vascular resistance <800 dyn s/cm^5, a cohort of patients with vasoplegia secondary to advanced CS or cardiometabolic syndrome, may have been excluded from this study. Lastly, mortality information was collected from available hospital records. Since there exists the possibility that all deaths may not have been adequately captured, an underestimation of actual mortality rates is possible.

CONCLUSIONS

VCS is associated with poor short- and long-term outcomes similar to other forms of CS. Eligibility for surgical or percutaneous intervention was associated with improved mortality compared to being offered medical therapy alone. Definitive surgical therapy and expansion of the role of percutaneous and surgical therapies are needed to optimize the care of this high-risk group.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Venu Menon, Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA. E-mail: menonv@ccf.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: VCS occurs most commonly due to native valve dysfunction, commonly involves aortic valve and is associated with worse short term and 1-year survival compared to other forms of CS. Definitive treatment in the form of surgery or percutaneous therapy should be pursued when possible.

TRANSLATIONAL OUTLOOK: The creation of reliable predictive models to assess candidacy for definitive therapy in patients with VCS should be further explored.

REFERENCES

1. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American heart association. *Circulation*. 2017;136(16):e232-e268. https://doi.org/10.1161/CIR.0000000000000525

2. Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol*. 2017;69(3):278-287. https://doi.org/10.1016/j.jacc.2016.10.022

3. Jentzer JC, Rayfield C, Soussi S, et al. Advances in the staging and phenotyping of cardiogenic shock. *JACC Adv*. 2022;1(4):100120. https://doi.org/10.1016/j.jacadv.2022.100120

4. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med*. 1999;341(9):625-634. https://doi.org/10.1056/NEJM199908263410901

5. Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med*. 2012;367(14):1287-1296. https://doi.org/10.1056/NEJMoa1208410

6. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med*. 2017;377(25):2419-2432. https://doi.org/10.1056/NEJMoa1710261

7. Harjola VP, Lassus J, Sionis A, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock: clinical picture and outcome of cardiogenic shock. *Eur J Heart Fail*. 2015;17(5):501-509. https://doi.org/10.1002/ejhf.260

8. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American college of Cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2021;143(5):e35-e71. https://doi.org/10.1161/CIR.0000000000000932

9. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561-632. https://doi.org/10.1093/eurheartj/ehab395

10. Ferguson DW, Kiefaber RW, Ziegelman DS, Uphold RE, Jackson RS, Tabakin BS. Acute rupture of myxomatous mitral valve presenting as refractory cardiopulmonary arrest. *J Am Coll Cardiol*. 1987;9(1):215-220. https://doi.org/10.1016/S0735-1097(87)80103-1

11. Stout KK, Verrier ED. Acute valvular regurgitation. *Circulation*. 2009;119(25):3232-3241. https://doi.org/10.1161/CIRCULATIONAHA.108.782292

12. Nitsche C, Kammerlander AA, Knechtelsdorfer K, et al. Determinants of bioprosthetic aortic valve degeneration. *JACC Cardiovasc Imaging*. 2020;13(2):345-353. https://doi.org/10.1016/j.jcmg.2019.01.027

13. Apostolidou E, Beale C, Poppas A, Stockwell P, Ehsan A. A case of bioprosthetic mitral valve dysfunction, initially presenting with valve thrombosis followed by recurrent thrombosis and endocarditis. *CASE*. 2019;3(5):210-214. https://doi.org/10.1016/j.case.2019.05.005

14. Pollak P, Lim DS, Kern J. Management of severe aortic regurgitation in a patient with cardiogenic shock using a percutaneous left ventricular

assist device and transcatheter occlusion of the failed aortic valve homograft as a bridge to surgical valve replacement: percutaneous Circulatory Support in Severe AR. *Cathet Cardiovasc Interv*. 2014;83(1):E141-E145. https://doi.org/10.1002/ccd.24993

15. Bonnabeau RC, Lillehei CW. Mechanical "ball failure" in Starr-Edwards prosthetic valves. *J Thorac Cardiovasc Surg*. 1968;56(2):258-264. https://doi.org/10.1016/S0022-5223(19)42857-2

16. Tirilomis T. Acute thrombosis of mechanical bileaflet aortic valve prosthesis. *J Cardiovasc Dis Res*. 2012;3(3):228-230. https://doi.org/10.4103/0975-3583.98899

17. Biteker M, Duran NE, Gündüz S, et al. Thrombolysis of an acute prosthetic mitral valve thrombosis presented with cardiogenic shock under the guidance of continuous transoesophageal monitoring. *Eur J Echocardiogr*. 2009;10(3):468-470. https://doi.org/10.1093/ejechocard/jen336

18. Rosenbaum PR. Observational studies. In: *Observational studies. Springer Series in statistics*. New York: Springer; 2002:1-17. https://doi.org/10.1007/978-1-4757-3692-2_1

19. Akodad M, Schurtz G, Adda J, Leclercq F, Roubille F. Management of valvulopathies with acute severe heart failure and cardiogenic shock. *Arch Cardiovasc Dis*. 2019;112(12):773-780. https://doi.org/10.1016/j.acvd.2019.06.009

20. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364(23):2187-2198. https://doi.org/10.1056/NEJMoa1103510

21. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374(17):1609-1620. https://doi.org/10.1056/NEJMoa1514616

22. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380(18):1695-1705. https://doi.org/10.1056/NEJMoa1814052

23. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307-2318. https://doi.org/10.1056/NEJMoa1806640

24. Jung RG, Simard T, Kovach C, et al. Transcatheter mitral valve repair in cardiogenic shock and mitral regurgitation. *JACC Cardiovasc Interv*. 2021;14(1):1-11. https://doi.org/10.1016/j.jcin.2020.08.037

25. Piriou P, Manigold T, Letocart V, et al. Outcomes of emergency transcatheter aortic valve replacement in patients with cardiogenic shock: a multicenter retrospective study. *Cathet Cardiovasc Interv*. 2022;99(7):2117-2124. https://doi.org/10.1002/ccd.30194

26. Debry N, Kone P, Vincent F, et al. Urgent balloon aortic valvuloplasty in patients with cardiogenic shock related to severe aortic stenosis: time matters. *EuroIntervention*. 2018;14(5):e519-e525. https://doi.org/10.4244/EIJ-D-18-00029

27. Masha L, Vemulapalli S, Manandhar P, et al. Demographics, procedural characteristics, and clinical outcomes when cardiogenic shock precedes TAVR in the United States. *JACC Cardiovasc Interv*. 2020;13(11):1314-1325. https://doi.org/10.1016/j.jcin.2020.02.033

28. Tang GHL, Estevez-Loureiro R, Yu Y, Prillinger JB, Zaid S, Psotka MA. Survival following edge-to-edge transcatheter mitral valve repair in patients with cardiogenic shock: a nationwide analysis. *J Am Heart Assoc*. 2021;10(8):e019882. https://doi.org/10.1161/JAHA.120.019882

29. Vemulapalli S, Carroll JD, Mack MJ, et al. Procedural volume and outcomes for transcatheter aortic-valve replacement. *N Engl J Med*. 2019;380(26):2541-2550. https://doi.org/10.1056/NEJMsa1901109

30. Chhatriwalla AK, Vemulapalli S, Holmes DR, et al. Institutional experience with transcatheter mitral valve repair and clinical outcomes. *JACC Cardiovasc Interv*. 2019;12(14):1342-1352. https://doi.org/10.1016/j.jcin.2019.02.039

31. Carroll JD, Mack MJ, Vemulapalli S, et al. STS-ACC TVT registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76(21):2492-2516. https://doi.org/10.1016/j.jacc.2020.09.595

32. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312(2):162. https://doi.org/10.1001/jama.2014.7246

33. da Costa LPN, Palma JH, Barbosa Ribeiro H, et al. Transcatheter mitral valve-in-valve implantation: reports of the first 50 cases from a Latin American Centre. *Interact Cardiovasc Thorac Surg*. 2020;30(2):229-235. https://doi.org/10.1093/icvts/ivz265

34. Urena M, Vahanian A, Brochet E, Ducrocq G, Iung B, Himbert D. Current indications for transcatheter mitral valve replacement using transcatheter aortic valves: valve-in-valve, valve-in-ring, and valve-in-mitral annulus calcification. *Circulation*. 2021;143(2):178-196. https://doi.org/10.1161/CIRCULATIONAHA.120.048147

KEY WORDS **cardiac critical care, cardiogenic shock, percutaneous treatment, valve replacement or repair, valvular cardiogenic shock**

APPENDIX **For a supplemental table and figures, please see the online version of this paper.**